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Effects of lacosamide and carbamazepine on human motor cortex excitability: A double-blind, placebo-controlled transcranial magnetic stimulation study

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ABSTRACT

Purpose: Lacosamide (LCM) and carbamazepine (CBZ) are antiepileptic drugs both acting on neuronal voltage-gated sodium channels. Patch-clamp studies demonstrated significant differences in how LCM and CBZ affect neuronal membrane excitability. Despite valuable information patch-clamp studies provide, they also comprise some constraints. For example, little is known about effects of LCM on intracortical synaptic excitability. In contrast, transcranial magnetic stimulation (TMS) can describe drug-induced changes at the system level of the human cerebral cortex.
Methods: The present study was designed to explore dose-depended effects of LCM and effects of CBZ on motor cortex excitability with TMS in a randomized, double-blind, placebo-controlled crossover trial in healthy human subjects. Subjects received 600 mg CBZ, 200 mg LCM, 400 mg LCM or placebo preceding TMS measurements.
Results: Compared to placebo, TMS motor thresholds were significantly increased after carbamazepine and lacosamide, with a trend for a dose dependent effect of lacosamide. Both, carbamazepine and lacosamide did not affect TMS parameters of intracortical synaptic excitability.
Conclusions: TMS measurements suggest that lacosamide and carbamazepine predominantly act on neuronal membrane excitability.

1. Introduction

CNS effects of neuroactive substances can be tested non-invasively with transcranial magnetic stimulation (TMS). TMS can measure several functions of cortical excitability, such as axonal membrane excitability of pyramidal tract neurons, and distinct forms of intracortical synaptic excitability.[1] In addition to some in vitro or animal research, TMS can investigate brain functions at a more comprehensive network level. This approach has been used in the past to compare pharmaco-physiologic properties of antiepileptic drugs of known action with newer substances, some with incompletely understood pharmacological mechanisms or multiple modes of action.[2–5]

Here we explored dose-depended effects of lacosamide (LCM) and effects of carbamazepine (CBZ) on motor cortex excitability with TMS in a randomized, double-blind, placebo-controlled crossover trial in young healthy human subjects. It was found in vitro that LCM selectively enhances slow inactivation of voltage-gated sodium channels, and, in contrast to CBZ, does not affect steady-state fast inactivation.[6] This mechanism of LCM to modulate sodium channels leads to normalization of activation thresholds and reduced pathophysiological hyper-responsiveness, without affecting physiological activity.[7] Therefore, it is thought that LCM, compared to CBZ, will be better tolerated by patients while being as or even more effective in controlling seizure activity.

On the basis of the results from nonhuman studies, we hypothesized that the TMS profiles of LCM and CBZ could be divergent. The idea behind this approach is not to use TMS to distinguish between fast and slow sodium channel inactivation, but to search for differential effects of the two drugs on the system level, that studies on the cellular level were unable to detect. CBZ, like other 'classical' sodium channel blockers such as phenytoin, predominantly demonstrated increased TMS motor thresholds indicating reduced neuronal membrane excitability, without developing significant changes of synaptic intracortical inhibition and facilitation.[4,8,9] Because of its novel mode of action it could only be speculated which TMS parameters LCM might affect. More than exclusively affecting neuronal membrane excitability, LCM could possibly also affect inhibitory mechanisms such as short-latency intracortical inhibition[10] or stimulation-induced excitability changes.[11,12] This would be in line with other well-tolerated modern antiepileptic drugs.[2,4,5,13]

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2. Materials and methods

2.1. Subjects

Fifteen healthy young men (mean age 26 ± 0.9 years; age range 19–32 years) gave their written informed consent to participate in the study. Women were not included due to potential medication risks in case of pregnancy. None of the subjects had any neurological or psychiatric disorder, as evaluated by certified medical specialists with experience in neurology (NL and HR). Further contraindications were: cardiac disorders; known hypersensitivity against lacosamide, carbamazepine, azoic dye or tricyclic antidepressants; acute intermittent porphyria; bone marrow disorders; implants in the head; drug or alcohol abuse; intake of any other medication and participation in another clinical trial within the previous 8 weeks. All subjects were consistent right-handers. Experimental procedures were approved by the Ethics Committee of the University of Kiel (Germany) and by the German Federal Institute for Drugs and Medical Devices (Bundesinstitut fuer Arzneimittel und Medizinprodukte, BfArM), and the study was performed according to the ethical standards laid down in the Declaration of Helsinki. The study was supported by a grant from UCB Pharma GmbH in Monheim (Germany), monitored by the Center for clinical studies (Zentrum fuer klinische Studien, ZKS) in Kiel and registered under www.ClinicialTrials.gov (NCT01382017).

2.2. Experimental design

The study was performed in a double-blind placebo-controlled cross-over design. All fifteen subjects participated in four drug conditions, separated by at least 1 week. Uniform capsules, containing 200 mg LCM, 100 mg LCM, 300 mg CBZ or placebo, were orally administered 12 and 2 h before TMS measurements (Fig. 1). This procedure has been used previously,[2,14] since serum concentrations and CNS effects can be expected to peak by the time of TMS measurements.[15,16] The order of drug conditions was pseudorandomized and balanced between subjects, and subjects and examiners were both blinded for them. TMS experiments were all performed on the left primary motor cortex (M1) and at identical times during morning hours with the subjects comfortably seated in a reclining chair with head and arm rests. Surface EMG from the right first dorsal interosseus muscle (FDI) was recorded through two Ag–AgCl surface electrodes placed over the muscle belly and the tendon. Raw signals were amplified, band-pass filtered (3 Hz–2 kHz) and sampled at 5 kHz by a PC attached to a micro 1401 AD converter (Cambridge Electronic Design, Cambridge, UK) controlled by Signal Software (Cambridge Electronic Design, version 4.08). Muscle relaxation was controlled by auditory and visual feedback. Single- and paired pulse TMS was performed by using a Magstim figure-eight-shaped 70-mm coil connected to Magstim Bistim[2] setup (Magstim Co., Dyfed, UK). The TMS coil was held over the left M1 with the handle pointing posterior and lateral. The induced electrical field of this coil positioning is optimal for a transsynaptic activation of the corticospinal system.[17] The optimal site for eliciting motor-evoked potentials (MEPs) in the resting right FDI was marked with a skin marker to ensure that the coil was constantly held correct during the experiment.

2.3. TMS measurements of cortical excitability

In each experimental session we measured the individual resting motor threshold (RMT), active motor threshold (AMT), the intensity to evoke MEP of ~1-mV peak-to-peak amplitude (SI1mV), short-interval intracortical inhibition/intracortical facilitation (SICI/ICF), recruitment curves (REC) and cortical silent periods (CSP).

Stimulus intensities (in percentage of maximal stimulator output) of TMS were determined at the beginning of each experiment. SI1mV was determined with single-pulse TMS first. RMT was determined using the maximum likelihood threshold hunting procedure[18] when the first dorsal interosseus muscle was completely relaxed. For AMT we used the lowest TMS intensity at which 50% of the stimuli elicited reliable MEP of approximately 200 μV in amplitude in the tonically contracting FDI.[19] For SICI/ICF two magnetic stimuli were given through the same stimulating coil in random order at 0.25 Hz.[10] The intensity of the conditioning stimulus was set to 90% AMT and the test-stimulus intensity to SI1mV. For SICI we used interstimulus intervals (ISI) of 2 ms and 4 ms, and for ICF ISIs of 9 ms and 12 ms. The control condition (test pulse alone) was applied 40 times, and each of the conditioning-test stimuli 20 times. The mean peak-to-peak amplitude of the conditioned MEP at each ISI was expressed as a percentage of the mean peak-to-peak size of the unconditioned test pulse. Mean SICI was defined as the mean percentage inhibition at ISIs of 2 and 4 ms, whereas mean ICF was defined as the mean facilitation at ISIs of 9 and 12 ms. Recruitment curves were measured with ten increasing stimulus intensities (90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, and 180% of RMT), each with 8 pulses. A mean was calculated for each intensity. At the end of each session, 10 pulses with SI1mV and 10 pulses with 120% RMT were applied under tonic contraction of the right first dorsal interosseus muscle. Out of these recordings CSPs were calculated in rectified and averaged EMG traces with a prestimulus period of 100 ms. We measured the CSP (in ms) from the TMS stimulus artefact to the point where the EMG signal reached the amplitude of the mean prestimulus EMG activity again for more than 5 ms.

2.4. Data analyses

The measures motor thresholds, SICI/ICF, recruitment and CSP were analyzed with separate analyses of variance (ANOVAs) for

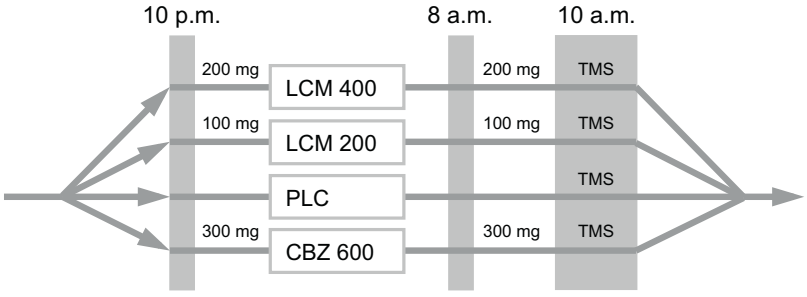

Fig. 1. Experimental design. Fifteen healthy volunteers received 200 mg or 400 mg lacosamide (LCM200, LCM400), 600 mg carbamazepine (CBZ600) or placebo (PLC) in a double-blind cross-over design. Half of the dose was taken 12 h and half of it 2 h before motor cortical excitability was examined with transcranial magnetic stimulation (TMS).

repeated measurements by using the mean values from each subject as the dependent variable. Besides the factor "drug" (LCM200 vs. LCM400 vs. CBZ vs. PLC), the ANOVA model included the factor "intensity" (AMT, RMT, SI1mV) when motor thresholds were analyzed, or "ISI" (2, 4, 9, and 12 ms) when SICI/ICF was analyzed, or "intensity" (90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, and 180% of RMT) for recruitment curves, or "intensity" (120% RMT and SI1mV) when CSPs were analyzed. For motor thresholds and SICI/ICF means were calculated of individual AMT, RMT and SI1mV values (mean motor threshold), and of the individual 2 and 4 ms ISIs (mean SICI) or 9 and 12 ms ISIs (mean ICF), respectively. When necessary the Greenhouse–Geisser method was used to correct for nonsphericity. Dependent on a significant F value, post hoc analyses were performed with paired samples two-tailed t-test, and a p value of <0.05 was considered significant for all statistical analyses. Data are expressed as mean ± SEM.

3. Results

Study medication was generally well tolerated. Subjects reported altogether 14 transient adverse events after drug administration in 60 experimental sessions, all being rated mild to moderate and all resolving spontaneously within 6 h. Transient adverse events (n per drug condition) were tiredness (PLC = 2, CBZ 600 = 3, LCM 400 = 3), nasopharyngitis (PLC = 1, LCM 400 = 1), oral dysaesthesia (LCM 400 = 1), headache (LCM 400 = 1), apathy (LCM 400 = 1) and hypacusis (PLC = 1). None of these adverse events interfered with the ability of the subjects to complete the study.

Effects of the four drug conditions on TMS motor thresholds are summarized in Table 1. ANOVA on motor thresholds revealed significant main effects for "drug" ($F_{(3,42)} = 10.6$, $p < 0.001$), "intensity" ($F_{(2,28)} = 78.9$, $p < 0.001$), and for the interaction "drug" by "intensity" ($F_{(6,84)} = 2.9$, $p = 0.012$). Post hoc comparisons demonstrated that mean motor thresholds significantly differed for the following pairs: PLC vs. CBZ ($t = -5.5$; df = 14; $p < 0.001$), PLC vs. LCM200 ($t = -2.8$; df = 14; $p = 0.015$) and PLC vs. LCM400 ($t = -5.5$; df = 14; $p < 0.001$). The comparison of LCM200 vs. LCM400 revealed a trend for a dose-dependent effect of lacosamide on motor thresholds ($t = -2.0$; df = 14; $p = 0.067$). Effects of carbamazepine on motor thresholds did not significantly differ from those of lacosamide, regardless of the dosage (p values > 0.1) (Fig. 2). Significant effects were also found in separate post hoc comparisons on the three motor threshold parameters (RMT: PLC vs. CBZ ($t = -5.5$; df = 14; $p < 0.001$), PLC vs. LCM400 ($t = -5.3$; df = 14; $p < 0.001$); AMT: PLC vs. CBZ ($t = -4.0$; df = 14; $p = 0.001$), PLC vs. LCM200 ($t = -2.4$; df = 14; $p = 0.034$), PLC vs. LCM400 ($t = -4.1$; df = 14; $p = 0.001$); SI1mV: PLC vs. CBZ ($t = -4.8$; df = 14; $p < 0.001$), PLC vs. LCM200 ($t = -2.4$; df = 14; $p = 0.029$), PLC vs. LCM400 ($t = -3.5$; df = 14; $p = 0.03$).

All other analyses did not reach significance, indicating no differential drug effects for SICI/ICF ("drug": $F_{(3,42)} = 0.2$, $p = 0.860$, "ISI": $F_{(1,14)} = 50.7$, $p < 0.001$, interaction "drug" by "ISI": $F_{(3,42)} = 3.1$, $p = 0.165$), recruitment curves ("drug": $F_{(3,42)} = 1.2$, $p = 0.315$, "intensity": $F_{(9,126)} = 94.6$, $p < 0.001$, interaction "drug" by "intensity": $F_{(27,378)} = 1.9$, $p = 0.139$), and cortical silent periods ("drug": $F_{(3,42)} = 0.7$, $p = 0.527$, "intensity": $F_{(1,14)} = 0.2$, $p = 0.675$, interaction "drug" by "intensity": $F_{(3,42)} = 1.7$, $p = 0.2$).

Table 1
Mean values (in % of maximal stimulator output) for active motor thresholds (AMT), resting motor thresholds (RMT), the intensities necessary to evoke MEP of ~1-mV peak-to-peak amplitude (SI1mV) and mean motor thresholds (∅MT), given for all four drug conditions (PLC, placebo; CBZ, carbamazepine 600 mg; LCM200, lacosamide 200 mg; LCM400, lacosamide 400 mg).

	AMT	RMT	SI1mV	∅MT
PLC	31 ± 1%	43 ± 2%	51 ± 2%	43 ± 2%
CBZ	34 ± 1%	47 ± 2%	58 ± 3%	48 ± 2%
LCM200	33 ± 1%	45 ± 2%	56 ± 4%	46 ± 3%
LCM400	34 ± 1%	48 ± 2%	58 ± 4%	48 ± 3%

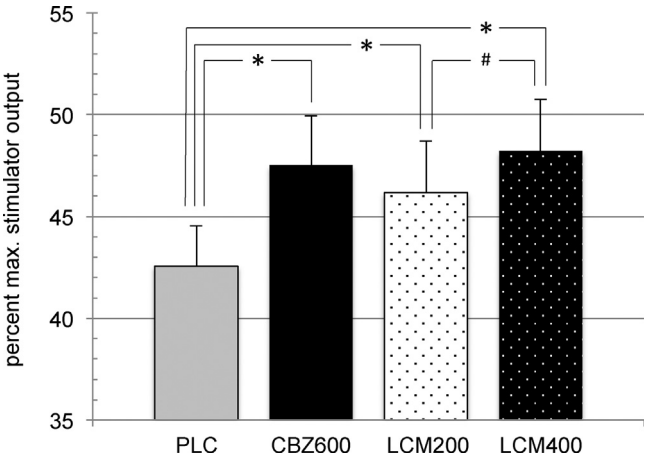

Fig. 2. Compared to placebo (PLC), the intake of 600 mg carbamazepine (CBZ), 200 mg lacosamide (LCM200) or 400 mg lacosamide (LCM400) led to significantly higher mean motor thresholds (asterisks indicating $p < 0.05$). Analyses revealed also a trend towards a dose dependent effect of lacosamide (hash, $p = 0.067$).

4. Discussion

Here we used TMS to investigate acute effects of lacosamide and carbamazepine on human motor cortex excitability. The results demonstrate that both, lacosamide and carbamazepine, significantly increase TMS motor thresholds compared to placebo. Analyses revealed no significant difference between threshold changes after lacosamide and carbamazepine, but showed a trend for a dose-dependent effect of lacosamide with higher thresholds after 400 mg lacosamide compared to 200 mg. Other TMS parameters of cortical excitability, such as intracortical inhibition and facilitation or cortical silent periods, were not altered after acute intake of both antiepileptic drugs.

Motor thresholds are global measures of corticospinal excitability, reflecting neuronal membrane excitability.[20,21] In patch-clamp studies phenytoin and carbamazepine block the inactive form of closed sodium channels,[22,23] and in the human corticospinal tract both substances increase motor thresholds, without pronounced effects on intracortical inhibition or facilitation.[4,9] In contrast to carbamazepine, lacosamide selectively enhances slow inactivation of voltage-gated sodium channels without affecting fast inactivation.[7] However, in the present study a differential effect compared to carbamazepine could not be demonstrated with means of TMS. Both lacosamide and carbamazepine developed clear effects on neuronal membrane excitability, without affecting synaptic excitability parameters.

Our results basically confirm previous studies on CBZ,[4,24] apart from a missing effect on CSP in the present study that may be due to different methodological approaches. Regarding TMS physiology they are in good line with results on other antiepileptic drugs that interact with voltage-gated sodium channels, not only phenytoin and carbamazepine, but also 'modern' antiepileptic drugs like oxcarbazepine[25] and lamotrigine.[26] Since the mechanism of action of oxcarbazepine is considered more or less 'classical' sodium channel blockade, it may not be surprising that its TMS profile resembles that of phenytoin and carbamazepine. Unlike lamotrigine, that shows a similar TMS profile, but differs substantially in its clinical use. Despite its sodium channel blocking mechanism, lamotrigine often appears to be a good treatment

Table 2
Comparison of acute antiepileptic drug effects (ordered by their main target structure) on different cortical excitability parameters tested with transcranial magnetic stimulation (TMS). (▲) Increase, (▼) decrease, (○) unchanged; CBZ, carbamazepine; OXC, oxcarbazepine; PHT, phenytoin; LTG, lamotrigine; LCM, lacosamide; GBP, gabapentin; PGB, pregabalin; DZP, diazepam; VGB, vigabatrine; TGB, tiagabine; VPA, valproate; LEV, levetiracetam; TPM, topiramate.

		MT	SICI	ICF	CSP	Reference
Sodium channel	CBZ	▲	○	○	○	Ziemann et al.[4]
	OXC	▲	○	○	○	Kimiskidis et al.[25]
	PHT	▲	○	○	○	Chen et al.[9]
	LTG	▲	○	○	○	Boroojerdi et al.[26]
	LCM	▲	○	○	○	Present study
Calcium channel	GBP	○	▲	▼	▲	Rizzo et al.[40] and Ziemann et al.[4]
	PGB	○	▼	○	▲	Lang et al.[11]
GABA-A receptor	DZP	○	▲	▼	▼	Inghilleri et al.[13]
	VGB	○	○	▼/○	○/▲	Pierantozzi et al.[44]
	TGB	○	▼	▲	▲	Werhahn et al.[39]
Other	VPA	○	○	○	○	Ziemann et al.[37] and Zunhammer et al.[45]
	LEV	▲	○	○	○	Reis et al.[33] and Sohn et al.[3]
	TPM	○	▲	▼	○	Reis et al.[5]

option for patients with idiopathic generalized epilepsies,[27,28] although many of these patients do not tolerate carbamazepine or phenytoin[29,30]; and even levetiracetam, which binds to the synaptic vesicle protein SV2A[31] and does seem to not interact directly with sodium channels,[32] leads to increased TMS motor thresholds.[33] Therefore, it can be concluded that under the TMS parameter 'motor threshold' different physiological and pharmacological mechanisms are subsumed, and drug-induced changes of this parameter do not predict whether an agent could be appropriate or inappropriate for certain epilepsy syndromes. This is in line with first reports indicating that lacosamide may also be tolerated in generalized epilepsies,[34,35] despite having a TMS profile similar to carbamazepine.

Our results do not indicate that lacosamide or carbamazepine alter intracortical synaptic excitability, such as SICI/ICF or CSPs. While SICI/ICF reflects excitability of inhibitory and excitatory cortical interneurons, primarily of the glutamatergic and GABA-A circuits,[4,9,36,37] CSPs involve GABA-B-receptor activity.[38,39] None of these mechanisms seems to be affected by lacosamide and carbamazepine. Other antiepileptic drugs can alter intracortical synaptic excitability (SICI/ICF and CSPs), e.g. gabapentin and pregabalin,[2,4,40] which are regarded as modulators of calcium channel activity, or topiramate,[5] which has many known mechanisms of action, such as enhanced GABA-mediated inhibition, inhibition of voltage-gated sodium channels, enhanced potassium channel conduction, inhibition of calcium channels, decrease of glutamate-mediated excitatory neurotransmission and carbonic anhydrase inhibition. For most antiepileptic drugs multiple mechanisms of action could be described by cellular physiology, mostly by using patch-clamp technique. However, it can be expected that further mechanisms exist and are still unknown. Interestingly, the profiles described with cellular physiology often do not match those described with TMS, and substances that seem similar in one way, appear different in the other (Table 2). For the clinician this divergence supports the experience, that when choosing optimal treatment for epilepsy patients mechanisms of actions are rather secondary.

TMS studies on pharmacodynamics of antiepileptic drugs are not free of limitations. These may lie in the result's transferability from healthy subjects to patients, since patients can show different responses to TMS or drugs compared to healthy controls,[41,42] or in the approach of a short-term drug administration, which can produce effects different from responses of the human brain to a drug administered over the long term.[8,43] On the other hand, TMS allows exploring noninvasively the mode of action of a drug in the intact human and comparing the pattern of excitability changes with those induced by other agents. In addition to cellular physiology, TMS can describe qualitative and quantitative changes at the system level of the human cerebral cortex. Our knowledge about pharmacokinetics of new antiepileptic drugs or substances with possible use as antiepileptic drugs in the future, such as perampanel or briveracetam, will benefit from this comparative research.

In conclusion the present study demonstrates that lacosamide mainly acts on neuronal membrane excitability. TMS, which can be useful to examine drug effects on the system level of the human motor cortex, did not show lacosamide-induced changes of intracortical synaptic excitability and no significant difference to effects induced by carbamazepine. This does not contradict results obtained with methods of cellular physiology.

Conflict of interest statement

Dr. Lang has received a research grant from UCB, travel grants from UCB and Eisai, speakers honoraria from UCB, Eisai, Desitin and Medtronic and has served as a paid consultant for UCB and Eisai. Dr. Rothkegel has received travel grants from UCB and Eisai and served as a paid consultant for Eisai. Dr. Deuschl has received lecture fees from Orion, Lundbeck, Teva and Pfizer and has been serving as a consultant for Teva. He received royalties from Thieme publishers. He is a government employee and he receives through his institution funding for his research from the German Research Council, the German Ministry of Education and Health and Medtronic. H. Peckolt has no conflicts of interest.

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